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Comparing Cost-Effectiveness Analyses of Anti-Hypertensive Drug Therapy for Decision Making: Mission Impossible?

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ABSTRACT

The purpose of this literature review was to compare the methodology used in the most recently published cost-effectiveness studies of antihypertensive treatments, and to identify methodological strengths and weaknesses that indicate the study's potential as a useful, decision-making tool. Based on the results of a search of several databases, spanning the years 1995 to 2000, 10 cost-effectiveness studies were identified. Although the majority of the studies reported their cost-effectiveness ratio in "costs per year of life gained," the studies also considered a varying range of components including additional end points. The methodology used to measure effectiveness, the cost variables included, and the characteristics of the patient population varied significantly across studies. Due to this lack of conformity, it would be difficult, if not impossible, to compare the results and draw conclusions about the relative cost-effectiveness of different types of antihypertensive drug therapies. This lack of uniform comparison across studies is likely to draw criticism from both the clinical and health-care decision-making communities. Future studies within this field should be thorough and useful for decision making. It is suggested that short-term outcomes should include systolic and diastolic blood pressure measurements and long-term outcomes should include end points such as myocardial infarction, stroke, congestive heart failure and renal events. Other positive outcomes such as a more favorable side-effect profile, should be used to enhance the primary outcomes. Additionally, when subpopulations are considered in submodels, studies should address the issue of generalizability. Cost calculations should be transparent and related to the perspective of the study. Modeling the cost-effectiveness of a drug may be an acceptable method provided that data sources and assumptions are valid and transparent.
Keywords: cost-effectiveness, decision making, guidelines, hypertension.

Introduction

Cost-effectiveness analysis (CEA) of a drug treatment provides information on the associated outcomes including costs and the gained clinical benefits of the treatment. This information can be useful in decision-making processes, particularly in cases where limited resources need to be allocated among a variety of different drug treatments. The cost-effectiveness (CE) ratios calculated in a CEA can be ranked in order such that a decision maker can select the intervention with the lowest cost per clinical benefits gained [1]. This approach seems most logical and beneficial for making treatment decisions regarding the use of numerous agents available for hypertension therapy. Although this review focuses on current CE analyses of hypertension treatments, it may also provide valuable insight into the management of overall cardiovascular risk, rather than just the treatment of hypertension. Approximately 48 million Americans suffer from hypertension, which is about one fifth of the total US population [2]. Hypertension is defined as systolic blood pressure (SBP) of 140 mmHg or greater, diastolic blood pressure (DBP) of 90 mmHg or greater, or ongoing therapy with antihypertensive medication for a previous diagnosis of hypertension based on similar blood pressure criteria. Stage 1 hypertension is defined as SBP 140–159 mmHg or DBP 90–99 mmHg, stage 2 as SBP 160–179 mmHg or DBP 100–109 mmHg and stage 3 as SBP ≥ 180 mmHg or DBP ≥ 110 mmHg [3]. It should be noted that in 1998, hypertension entered the list of the 15 leading causes of death in the United States [4]. This condition is one of the major factors contributing to the development of cardiovascular diseases (CVD). CVD have been the leading cause of death for many years and in 1998 accounted for 31% of total mortality in the United States [4]. The combined direct and indirect cost of CVD and stroke in the United States in 2000 was estimated

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at $326.6 billion and accounted for the largest proportion of health care spending [5].

Reports from various stakeholder communities have argued that the current methods for calculating and reporting CE results for decision making are suboptimal [6–8]. The variability among the studies is a reflection of: 1) the fact that this is a new area of research; 2) the inherent variability within clinical data and clinical trials; and 3) the reality that there is a demand for health economic data early in the development process for pricing and reimbursement, while there is a need for long-term studies, particularly for chronic diseases. To address general issues related to pharmacoeconomic studies, The US Public Health Service set up a Panel on Cost-Effectiveness in Medicine and published a supplementary book, which summarizes discussions and recommendations set by the panel [1]. The Academy of Managed Care Pharmacy has published a set of guidelines for submission of clinical and economic data in support of formulary considerations to facilitate the use of pharmacoeconomic information for decision making [9]. Johannesson and Johnsson examined various methodological approaches that specifically affect the results of antihypertensive CEAs [10]. They found that results obtained from cost-effectiveness and outcomes research studies in the field of hypertension must be interpreted with caution. As the field of pharmacoeconomics is evolving, the objective of this paper is to analyze the most recent CE studies of treatments for hypertension. We assumed that these studies were meant to be informative to the decision-making process with respect to antihypertensive treatment options. Our intention was not to state whether the CEA was poor or strong but rather to identify those studies that actually performed a true CEA, i.e., considered both costs and effectiveness of hypertension treatment, and to identify differences and similarities across the study analyses.

Given the prevalence of hypertension and the cost burden that this disease poses to society if left untreated, many scholarly papers address the CE of hypertension treatments. Therefore, the first objective of this article is twofold: first to identify the number of articles that discuss or mention the CE of hypertension treatment, and second, to identify how many actually performed a CEA.

The second objective is to outline and discuss the methodology of the published CEA analyses of hypertension treatments. The third objective is to consider their limitations with respect to their influence on the decision-making process and the interpretation of results across studies. The overall goal is to provide guidance so that future CEAs of hypertension treatments will provide more optimal information for clinicians and other decision makers when choosing an antihypertensive treatment. It should be noted that this review focuses on the calculation and reporting of the cost-effectiveness estimates rather than on the actual numeric values derived from the cost-effectiveness analyses. Therefore this review should not be used to assess the cost-effectiveness of different antihypertensive drugs.

Methods

A search of the literature published between the years 1995 to 2000 was conducted using the following terms: hypertension (and) cost-effectiveness (or) economics. The following databases were consulted for this particular search: Medline; Health Star; International Pharmaceutical Abstracts; EBM reviews (Cochrane database); National Health Sciences Center for Review and Dissemination, University of York.

The quality of the cost-effectiveness calculation depends on the methodology applied and the accuracy and relevance of data used to calculate the benefit and cost measures. The following sections report the search result according to the type of patients studied, how effectiveness was measured or derived, how costs were measured, how the overall cost-effectiveness ratio was reported and what end points were used.

Results

Eighty-nine articles were identified as a result of our searches across various databases. Of these, 59 articles either discussed or mentioned the cost-effectiveness of hypertension treatment in various contexts but did not perform an actual cost-effectiveness analysis, and 19 articles were pure cost studies, which analyzed the cost of hypertension treatment within different clinical settings. These 78 articles were therefore excluded from our selection. The remaining 11 articles were true pharmacoeconomic studies. One of the 11 studies analyzed the cost-effectiveness of the diagnosis and therapy of renovascular hypertension [11]. This study was not included in the review since it focused primarily on the cost-efficacy of several different screening tests for renovascular hypertension. Therefore, only the 10 most relevant cost-effectiveness studies of drug treatment for hypertension comprised the

focus of this literature review [12–21]. These 10 studies are denoted STUDY1–10.

A problematic outcome of our analysis is the fact that there is considerable variation across antihypertensive CEA studies with respect to types of patients examined, the measures of effectiveness and costs used, and the way in which cost-effectiveness ratios were calculated and reported.

Patient Population

Table 1 presents the characteristics of the population in the clinical trials and/or the hypothetical population included in the models. The information in Table 1 is what was found in the corresponding CE study, which may not be as complete as what was described in the original clinical trial. Some of these studies presented the characteristics of the trial patients so that the reader did not have to go back to the original trial, while others did not. The studies differed in terms of both demographic and clinical characteristics. Some studies examined actual patients, while others modeled hypothetical cohorts of patients. Four of the cost-effectiveness studies based their work on clinical trials, which implies that they obtained treatment effects, incidence data and survival data from these trials [12–15]. STUDY2 [13] and STUDY3 [14] randomized their patients into groups of treatments with drug A vs. drug B and tight vs. less tight blood pressure control, respectively. STUDY1 [12] and STUDY4 [15] obtained measures of treatment effectiveness from clinical trials in which patients were randomized according to different diastolic blood pressure target groups and into groups of treatment vs. no treatment, respectively. The patient populations in the clinical trials all had concomitant diseases, although STUDY3 [14] excluded patients if they had a cardiovascular or cerebrovascular event within the 6-month period preceding the start of the trial.

In studies where researchers combined data from different sources and used modeling to project life expectancy, existing risk factors were accounted for by using a variety of techniques [17–19]. In one model it was assumed that hypertensive patients did not initially have any concomitant diseases [19]. This was also true for the model used in STUDY 5 except that the patients had type-2 diabetes [16]. STUDY9 [20] and STUDY10 [21] did not provide information about the population, but STUDY9 categorized patients as having moderate to severe hypertension or mild hypertension.

The majority of studies defined hypertension based on the diastolic blood pressure, which was used as an inclusion criteria [12,13,17,18,20,21]. STUDY8 [19] focused on the effect of treatment on systolic blood pressure alone, and the remaining studies, STUDY4 [15] and STUDY5 [16], required both elevated diastolic and systolic blood pressure measurements for inclusion (Table 1).

Effectiveness

With respect to the effectiveness component, STUDY2 [13] and STUDY3 [14] derived treatment effectiveness directly from the trial results (Table 2). STUDY1 [12] derived treatment effectiveness from the Hypertension Optimal Treatment (HOT) study and STUDY5 [16], from the Studies of Left Ventricular Dysfunction (SOLVD) trials, which included two clinical trials: the Treatment Trial, and the Prevention Trial. The remaining studies utilized results from several different clinical trials to estimate the treatment effect of various antihypertensive drugs [16–21]. Most of the studies discounted both the benefits and costs except for STUDY1 [12], which discounted the benefits but not the costs, since costs were annual. Neither benefits nor costs were discounted in STUDY3 [14] or STUDY10 [21] because they had short follow up periods, as indicated in Table 3.

Studies that used life years gained in the outcome measure generated life expectancy and/or survival estimate through the use of modeling. The models incorporated the treatment effect and the incidence data to estimate hypothetical longevity, assuming that a person was on lifelong antihypertensive treatment. Several studies used the Framingham risk equations to determine the pretreatment risk of cardiovascular disease and stroke, as indicated in Table 2 [17–20]. STUDY2 [13] used the differences in hazard rates between the two trial groups and assumed that the groups would have identical hazard rates beyond the trial [13]. Another study estimated the annual survival probabilities using data from two clinical trials and created a survival curve from which the life expectancy was estimated from the area under the curve [15]. STUDY4 [15], STUDY7 [18], and STUDY8 [19] adjusted the achieved life years gained for quality of life by applying a utility measure (Table 2).

Costs

Table 3 presents the cost variables included in the cost-effectiveness measure and the corresponding references. Only STUDY3 [14] derived costs entirely from the resources used during the clinical trial. STUDY2 [13] used resource units from the clinical trial but added cost information from

Table 1 Study population characteristics (information found in CE study)

Study no.	1 [12]	2 [13]	3 [14]	4 [15]	5 [16]
Type of population	C	C	C	C	H
N	Not provided	1148	120	1917	NA
Age, mean years (SD)	Not provided	56 (8.1)	55	Approx. 61 (9.4)	50–59, 60–69, 70–79, 80–89
Baseline DBP mmHg (SD)	Not provided	≥90 (no treatment)	95–115	Approx. 86.2 (8.9)	90
Baseline SBP mmHg (SD)	No focus on SBP	≥160 (no treatment) ≥150 (on treatment)	No focus on SBP Excluded if >200	Approx. 144.4 (12.6)	140
Male %	Not provided	54	39	Approx. 85	Not considered
Race %	Not provided	Not provided	Not provided	Approx. W: 79, B: 14, O:7	Not considered
Prior MI %	Not provided	Not provided	Excluded if MI within 6 months prior to study start	Approx. 70	None
Baseline CHD %	Not provided	Not provided	Excluded if CABG, CHF 6 months prior to study start	Approx. 26–74	None
Baseline CVD	Not provided	Not provided	Excluded if TIA 6 months prior to study start	Not provided	None
Baseline renal disease	Not provided	Not provided	Not provided	Not provided	None
Mention of diabetes	No	All had type 2	No	No	All had type 2
Mention of cholesterol	No	No	No	No	No
Mention of smoking	No	No	No	No	No
Study no.	**6 [17]**	**7 [18]**	**8 [19]**	**9 [20]**	**10 [21]**
Type of population	H	H	H	CH	H
N	NA	NA	NA	Not provided	NA
Age, mean years (SD)	<45, 45–69, >70	<45, 45–69, >70	Accounted for in model	39–69	Not considered
Baseline DBP mmHg	90–94, 95–99, 100–104	90–94, 95–99, 100–104	No focus on DBP	95–104, ≥105	≥93.5
Baseline SBP mmHg	No focus on SBP	No focus on SBP	180	No focus on SBP	No focus on SBP
Male %	Gender differences according to risk factors accounted for	All analyses carried out separately for men and women	Gender differences according to risk factors accounted for	Gender differences according to risk factors accounted for	Not considered
Race %	Not considered	Not considered	Not considered	Not considered	Not considered
Prior MI %	None	Not considered	None	Not provided	Not considered
Baseline CHD %	None: Existing LVH accounted for in model	Not considered: existing LVH accounted for in model	None	Not provided	Not considered
Baseline CVD	Not considered	Not considered	None	Not provided	Not considered
Baseline renal disease	None	Not considered	Not considered	Not provided	Not considered
Mention of diabetes	Glucose intolerance	Glucose intolerance	Accounted for in model	Accounted for in model	No
Mention of cholesterol	Accounted for in model	Accounted for in model	Accounted for in model	Accounted for in model	No
Mention of smoking	Accounted for in model	Accounted for in model	Accounted for in model	Accounted for in model	No

Abbreviations: B, black; C, clinical trial population (real people; reference to original trial was provided in the CE study); CABG, coronary artery bypass graft; CH, cohort enrolled in a cardiovascular prevention program; CHF, congestive heart failure; DBP, diastolic blood pressure; H, hypothetical population; LVH, left ventricular hypertrophy; O, other; SBP, systolic blood pressure; TIA, transient ischemic attack; W, white.

Table 2 Reported cost-effectiveness results, end points, treatment comparison, method of deriving benefit measure, treatment duration, and follow-up time for events

Study no.	1 [12]	2 [13]	3 [14]	4 [15]	5 [16]
Costs per life year gained	$4,262–$658,370	£291–£720 (incremental)		<5% chance that cost >$3,000	$(8,236) savings–$1,664
Incremental cost per mmHg reduction			4 Swedish crowns		
Event cost saving per person year					
Cost per QALY				$2,660	
Other benefits	MI averted	Extra years free from end points	Number of patients reaching target DBP		Avoided morbid events, Incremental medical therapy to reach BP goal
End points	Fatal MI	CHD, cerebrovascular disease, amputation, laser surgery for retinopathy, cataract extraction, renal failure, death	mmHG reduction	Combined heart disease, hospitalization for heart failure, death	MI, stroke, heart failure, end stage renal disease, death
Treatment comparison	Three BP reduction target groups	Two BP reduction target groups	CCB/BB vs. ACEI	ACEI vs. placebo	Two BP reduction target levels
Treatment effects	3.6 MI/1,000 person years 2.7 MI/1,000 person years 2.6 MI/1,000 person years	Years free from end points within trial	CCB/BB = 12 mmHg reduction ACEI = 7.2 mmHg reduction	0.819 relative risk (RR) reduction for mortality	RR = 0.65 (stroke), 0.90 (MI), 0.80 (ESRD), RR = 0.75 (heart failure)
How the treatment effect and benefit measures were derived	Clinical trial; modeled years of life lost	Clinical trial; simulation model to estimate life expectancy	Clinical trial	Clinical trial; state transition model to project survival	Published studies; Markov model to estimate survival time
Drug treatment duration	Not reported	8.4 years (range 0–10)	8 weeks	Approx 2.8 years	Not reported
Follow-up time for events	Not reported	8.4 years (range 0–10)	4 and 8 weeks	Approx 2.8 years	Lifetime

(continued)

Table 2 continued

Study no.	6 [17]	7 [18]	8 [19]	9 [20]	10 [21]
Costs per life year gained	M: 947,000 Swedish crowns F: 2,506,000 Swedish crowns	M: $1,000–$112,000 F: $0–$250,000	BB1: 30,000–24,000 New Zealand $ BB2: 22,500–14,000 New Zealand $	M: $31,527–$68,246 F: $28,858–$126,990	
Incremental cost per mmHg reduction					
Event cost saving per person years					CHD: $45.76 Stroke: $21.64
Cost per QALY		$1,000–$172,000	Approx equal to cost per life year gained due to low incidence of nonfatal events during 5-year treatment period		
Other benefits					
End points	CHD, Stroke	CHD, stroke, death	CHD, cerebrovascular event, death	Morbidity and mortality due to BP level	CHD, Stroke
Treatment comparison	CCB/ACEI vs. BB/diuretic vs. placebo	N/A	BB1 vs. BB2	CCB vs. ACEI vs. BB vs. diuretic	ACEI1 vs. ACEI2 vs. ARB
Treatment Effects	BB/diuretic: RR = 0.38 (stroke), 0.16 (CHD) CCB/ACEI: RR = 0.38 (stroke), 0.23 (CHD)	All treatments: RR = 0.38 (stroke), 0.16 (CHD)	SBP reduction: BB1 = 14.4 mmHg BB2 = 16.0 mmHg	mmHG DBP reduction: Mild HTN: 4.9–10.0 Moderate HTN: 13.4–21.4	DBP trough/peak ratio: 55%–87.5% Peak DBP = 10 mmHg for each drug
How the treatment effect and benefit measure were derived	Meta-analysis: logistic risk function for stroke + CHD from Framingham study	Meta-analysis: logistic risk function for stroke, CHD and survival from Framingham study	Meta-analysis: modeled prediction of 5-year reduction in absolute risk using drug data and Framingham data	Applied Farmingham equation to cohort study morbidity and mortality data	BP peak ratios to estimate BP control; modeled the risk of events using published data
Drug treatment duration	Not reported	Not reported	5 years	Not reported	1 year
Follow-up time for events	Not reported	Not reported	5 years	Not reported	6 to 25 years (mean 10)

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor antagonist; BB, beta blocker; BP, blood pressure; CCB, calcium channel blocker; CHD, coronary heart disease; DBP, diastolic blood pressure; ESRD, end-stage renal disease; F, female; HTN, hypertension; M, male; MI, myocardial infarction; QALY, quality-adjusted life year; SBP, systolic blood pressure.

Table 3 Study perspectives, cost components, cost data source, discounting and use of sensitivity analysis

Study no.	1 [12]	2 [13]	3 [14]	4 [15]	5 [16]
Perspective	Societal (direct costs only)	Third-party payer	Third-party payer	Third-party payer	Third-party payer
Cost components	Drugs, office visits, laboratory work	Drugs, home visits, hospital	Drugs	Drugs, hospital	Drugs, inpatient care, nursing home
Source of cost data	Average drug wholesale price, published studies	Trial centers, British government	Trial resource use (calculated)	Unit costs from trial, federal reimbursement rates, surveys	Federal reimbursement rates, annual costs from other studies
Discounting (costs/ effectiveness)	No / Yes	3% and 6% for both	No / No	5% / 5%	5% / 5%
Sensitivity analysis	No	Alternative discount rates and no. of office visits	Alternate drug prices	Alternative treatment costs and discount rates at 2% and 7%	Alternative ages at which patients initiated treatment
Study no.	6 [17]	7 [18]	8 [19]	9 [20]	10 [21]
Perspective	Societal	Societal	Limited societal (direct costs only)	Not stated (direct costs only)	Third-party payer
Cost components	Drugs, consultations, travel and time, productivity losses	Drugs, consultations, travel and time, morbidity, surgery and diagnostics, increased healthcare costs, production losses, net consumption	Drugs, consultations, outpatient visits, ambulance, costs per event, hospital stay, rehabilitation	Drugs, office visits, laboratory and screening tests	Drugs, costs per event
Source of cost data	Published studies	Published studies, Swedish labor department, payroll tax	New Zealand unit drug costs, published studies	Spanish social security system	Drug wholesale price, published studies
Discounting (costs/ effectiveness)	5% / 5%	3% / 3%	5% / 5%	5% / 5%	No / No
Sensitivity analysis	No	Alternative assumptions about treatment benefit costs and quality of life	Used discount rate at 11.4%	No	Alternative event costs

sources outside the trial. The remaining studies all derived their cost information from a variety of sources, including published studies and government reports.

Eight studies used a third-party payer perspective and included only direct health-care costs, which usually are the costs of drugs, office visits, laboratory tests and hospital admissions (Table 3) [12–16,19–21]. Some studies included only a subset of these direct cost variables. STUDY9 [20] did not state the perspective and STUDY8 [19] stated its perspective as a limited societal perspective, as the direct costs paid by the government and the patients themselves were included. STUDY4 [15] stated that societal costs were evaluated, as the costs were derived solely from federal reimbursement agencies. However, the cost variables included in the study implied that the perspective was that of a third party payer.

Two studies used the societal viewpoint and included productivity loss, measured by income, for the indirect cost component [17,18]. One of the studies also considered increased health-care costs due to morbidity as part of the indirect costs and included future costs in terms of increased consumption net of production [18]. Of the 10 studies, three did not discount the costs, which is reasonable for both STUDY3 [14] and STUDY10 [21] since the duration of follow up was short (Table 2) [12,14,21]. The majority of studies included sensitivity analyses, either by varying the costs or the treatment effects or by varying the discount rates, as indicated in Table 3.

Reporting the Cost-Effectiveness Ratio (CER)

As shown in Table 2, most cost-effectiveness studies expressed cost-per-life-year-gained (saved) results as the outcome measure [12,13,15–20]. Two studies considered the incremental cost of clinical-related outcomes such as mmHg blood pressure reduction or extra year free from end points [13,14]. Other noted outcome measures were: cost per avoided morbid events [16]; cost of incremental medical therapy to achieve lower blood pressure goals [16]; event-reduction cost savings [21]; and costs per quality-adjusted life year [15,18,19]. Several studies provided multiple outcome measures [13–16,18].

The end points included in the analysis varied greatly across studies. Most studies included coronary heart disease, stroke and death as end points [13,16,18,19]. In addition to cardiovascular and cerebrovascular events, some studies included renal failure, end stage renal disease and heart failure as end points. STUDY2 [13] also extended the number of end points by including amputation, laser treatment for retinopathy and cataract extraction. STUDY9 [20] did not specify the actual end points other than "morbidity and mortality according to high blood pressure." While STUDY1 [12] only included death in terms of fatal myocardial infarction as the end point, STUDY6 [17] and STUDY10 [21] excluded death but included coronary heart disease and stroke. Only STUDY4 [15] included hospitalization for heart failure and a measure consisting of a number of ischemic events as end points. STUDY3 [14] used mmHg-reduced blood pressure during the trial period and a treatment target of diastolic blood pressure less than 90 mmHg as end points. Table 2 also presents the cost-effectiveness results and the drug comparisons performed within each study.

Discussion

Our findings stress that there is little methodological consistency across cost-effectiveness studies evaluating pharmacotherapy for the management of hypertension. There clearly exists a disparity between the approach and format that indicates a need for tighter comparison across studies. Studies considered different end points, and the methodology used to measure effectiveness, the cost variables included, and the characteristics of the patient population varied significantly across studies. Due to this lack of uniformity, it is difficult, if not impossible, to compare the results and draw conclusions about the relative cost-effectiveness of different types of drug therapies. This lack of comparability between studies is likely to elicit criticism from both the clinical and health-care decision-making communities, and is likely to undermine the argument supporting wider use of cost-effectiveness analyses in health-care decision making. In the following sections we explore the major points that emerged from our research findings as they relate to the viability of economic evaluations in health-care decision making, although the issues discussed are not relevant to every study included in this review.

Patient Population

The modeled population considered in economic evaluations must reflect a population in a naturalistic health-care setting to ensure practicability and generalizability of results. Pharmaceutical benefit management (PBM) companies support the principle that relevant populations in CEA make the analysis more useful for formulary decision making [6]. Limitations to the generalizability of economic

studies are more often due to the clinical design of the studies, namely patient inclusion and exclusion criteria, than to methodological flaws in the economic analysis. Therefore, generalizability of the study to other patient populations should be addressed either by using modeling or by addressing the issue as part of the discussion.

When performing economic evaluations of subpopulations defined in terms of gender, race, age groups, and/or the presence of certain comorbidities, researchers should, to the extent possible, present the results in the same context as the full analysis. Sub-analyses usually compare the benefits of one agent vs. another in a selected group of patients, which is a legitimate and valid method. However, the end points should generally be consistent with the ones used when the analysis is applied to the general population (i.e., measured in terms of reduction in a consistent set of major end points – cardiovascular, stroke, or renal events). For this reason, subanalysis should conform to the overall analyses to make comparability across studies meaningful. In turn, this procedural recommendation should not be construed as restricting the evaluation of a particular antihypertensive agent for the purposes of showing superiority over other agents in terms of a specific end point. For example, angiotensin converting enzyme (ACE) inhibitors have been documented as being superior to other antihypertensive agents in terms of renal protective effects in hypertensive, diabetic patients. While cost-effectiveness analysis in this case is legitimate and quite valuable, conducting the cost-effectiveness analysis as a subanalysis should address the issues relevant to general hypertensive patients as well; namely, the cost components, outcomes, and appropriate drug comparators. Otherwise, the authors should be very clear and direct about the lack of generalizability of their results.

Despite the fact that isolated SBP is a better predictor of cardiovascular and cerebrovascular outcomes as compared to isolated DBP [22], the majority of studies defined hypertension in terms of diastolic blood pressure and used baseline diastolic blood pressure as an inclusion criterion. This may be due in part to the fact that the importance of SBP is a rather recent finding. Nevertheless, future studies should address both the SBP and the DPB when defining hypertension and the inclusion criteria for clinical trials.

Cost Components

As presented in Table 3, cost components vary significantly across the studies and many studies pooled economic data from multiple study sites or federal reimbursement sites. This methodology could pose a problem if appropriate adjustments are not made, since practice patterns differ among providers according to their site (rural, suburban or urban), and according to whether it is the Veterans' Administration or a managed care setting or whether costs are derived directly from clinical trials [23].

STUDY2 [13] addressed the issue of resource utilization by considering resources driven by the trial protocol and resources driven by standard clinical practice. The problem with using divergent sources becomes even more serious when cost data are collected from different countries, as currency conversions add to the uncertainty [23]. STUDY7 [18] and STUDY9 [20] converted cost estimates into US dollars from Swedish Crowns and Spanish Pesetas, respectively. To minimize the uncertainty associated with health-care utilization, improved methods for estimating variance in resource utilization are required [23]. Sensitivity analysis that accounts for the variation in expenditures for health-care services is one method available for testing how the variability in utilization affects the cost-effectiveness of the treatment. Some methods used to translate cost estimates across countries include the use of exchange rates, purchasing power parity and discount rates, or price indexes when the time period differs across studies.

Economic evaluations in most of the studies were conducted from a payer perspective and considered only direct costs (Table 3). All relevant direct costs such as drugs, office visits and hospitalizations were usually included. Direct costs such as emergency room visits and nursing time that were not included should perhaps be considered in future studies to achieve a more thorough and accurate representation [23]. Only a few studies considered indirect costs, which are important both to the patient and to society. Furthermore, it is essential to include indirect costs in hypertension studies to capture all the relevant areas that a drug treatment may affect. In terms of therapeutic interventions for hypertension, whenever a hospital admission is prevented, the treatment also diminishes productivity losses, which the patient would have experienced due to absenteeism from work or reduced productivity while at work [24].

None of the studies considered the costs of switching from one drug or class of antihypertensive pharmacotherapy to another. Only one study accounted for costs due to side-effects [16]. STUDY5 [16] described an increase in the cost per

life year saved in direct proportion to the increased likelihood of an adverse event, or an increase in the ultimate costs of adverse events. However, the authors stated that they did not include additional costs for hospitalization and/or injuries due to adverse reactions, since those occurrences are very rarely associated with current antihypertensive drugs. These costs may be captured when treatment costs are derived fully or partially from the clinical trial. Poor compliance may also be associated with higher health-care costs [16,25]. Rizzo et al. [25] examined compliance rates for four major antihypertensive drug classes and the health-care costs associated with noncompliance. Compliance rates varied between drug classes, and poor compliance was associated with higher health-care costs [25]. In future studies it may be important to consider compliance, as suggested by Roth et al. [21], since poor compliance with pharmacotherapy is a very common phenomenon among antihypertensive patients.

Outcomes (End Points)

Although the end points included in the economic evaluations varied across studies, the majority of studies used a variety of hard clinical end points as the primary outcome, suggesting that a certain consensus has been achieved in terms of including cardiovascular and cerebrovascular events. Only two studies considered renal events as end points, specifically in the case of hypertensive-diabetic patients. Reducing blood pressure can, naturally, reduce the occurrence of both events contingent on the length of follow-up. Nonetheless, these hard clinical end points should be the ultimate goal and focus of economic analyses, rather than the reduction in blood pressure itself. The fact that the studies use diverse end points and approaches to calculate cost-effectiveness should not be attributed to flawed or faulty methodology, but rather, as evidence that pharmacoeconomic evaluations lack methodological consistency, particularly in the case of antihypertensive treatments. This reduces the utilitarian value of the results of these evaluations for health-care decision making. One way to address this issue is to define a priori primary and secondary outcomes of the CEA.

While we did not specifically address the differences in risk functions used and their consequences for the pharmacoeconomic outcomes presented here, it is worth stating that the studies also applied different statistical methods. Some have used log risk functions and clinical trial information (Table 2), while others used Weibull models. This complicates the comparison of pharmacoeconomic outcomes unless the authors specifically address such issues in their study.

Since most hypertension studies are of a short duration, the long-term benefits are often modeled. In the process of model development, it is important that uncertainties and assumptions are clearly stated [26]. The majority of studies used modeling to extend treatment benefit beyond the duration of the respective clinical trials. However, the information presented in some of the studies lacked the transparency necessary for the reader to determine whether the methods used were appropriate and whether the assumptions made were sound. For example, STUDY9 [20] mentioned that the effectiveness term of life year gained was estimated using the Framingham equation without describing the method. Likewise, the study did not address the duration of antihypertensive treatment from which the treatment effect is projected. Similarly, in STUDY1 [12] it is unclear how the net years of life gained were converted into disability-adjusted life years and further translated into cumulative disability-adjusted life years. Contrary to these examples, studies such as STUDY2 [13] and STUDY4 [15] clearly explain how they defined the treatment benefit and the method used to estimate life expectancy (Table 2). It is important that methods and assumptions be clearly presented so that decision makers can be confident when applying these results to their health-care system.

Modeling Long-Term Outcomes

Hay et al. [26] strongly recommended that modeling of costs and effectiveness attain greater recognition as a valid and often essential component of health-care decision making. In chronic diseases such as hypertension, outcome events such as complications of the disease or its treatment, recurrence of disease and mortality are often confounded with probabilities that change with time during a lifetime, such as age and health status. Thus, models that allow for a change in the risk of outcomes over time may be more informative and realistic.

Appropriate Drug Comparator

Multi-drug comparison is also expressed by PBM's as a need for economic evaluations [6]. It is widely accepted that lowering blood pressure reduces the risk of cardiovascular, cerebrovascular, and renal events. If health-economic evaluations of treatments for hypertension are to be useful for decision making, the evaluations should shift the focus from prevention of clinical end points by any drug to the

economic consequences of preventing clinical end points by a number of specific comparable drugs. Four studies compared the cost-effectiveness across two or more specific antihypertensive drugs [14,19–21]. In STUDY4 [15] drug-placebo comparison was performed, whereas STUDY6 [17] compared several antihypertensive drug categories such as ACE inhibitors plus calcium antagonists to beta blockers plus diuretics. The remaining studies did not consider a specific treatment but rather, examined the fact that drug treatment reduces blood pressure and thereby reduces the risk of specific clinical end points. Drug comparisons either within each of the antihypertensive drug classes or across the drug classes would be useful for the decision-making process.

Summary and Recommendations

Management of hypertension, regardless of the specific therapy, is targeted toward reducing the long-term outcomes, most importantly cardiovascular, cerebrovascular and renovascular events. It is true that all studies are conducted with different patient populations in terms of the inclusion and exclusion criteria, but all studies are performed on patients with hypertension stages I, II, and/or III. Alternatively, subanalyses can be performed on each patient subpopulation. Finally, a combination of modeling and subpopulation analysis can be applied, while accounting for the probabilities of the different end points among the different populations. Cost-effectiveness studies of antihypertensive therapies should maintain their focus on these primary outcomes. To the extent that other positive attributes, such as a more favorable side-effect profile, are considered, they should be viewed in the context of the primary objective of reducing cardiovascular events.

It is helpful to examine specific subpopulations of hypertensive patients, which may offer additional guidance to clinicians and other decision makers. When subgroups such as diabetic-hypertensive patients with elevated systolic hypertension, or a specific race or gender is examined, modeling techniques can be used to address these subgroups. Sub-analyses can be performed on each patient subpopulation, or a combination of these two methods, while accounting for the probabilities of the different end points among the different patient populations, can be applied. Again, subpopulation analysis should not focus on one isolated facet of hypertension management without addressing the broader concerns of general hypertension management, unless the agent is going to be indicated only for that specific particular aspect.

Determining which cost components to include and how to measure them is difficult. Variation may exist across patient populations or clinical practice settings. In most European countries for example, laboratory or diagnostics costs are included in the visit or hospitalization costs. Consequently, the cost components could be simplified into categories that are common to all drug classes. These common categories include: hospitalizations; physician services; office visits; emergency room visits; laboratory/diagnostics; drug costs (accounting for realistic compliance and switch therapy), and adverse events.

If economic analyses are performed while keeping in mind the issues described above, one can see that the analyses will then be more comparable. Decision makers can make more valid judgments as to the viability of a particular economic evaluation or the credibility of results. What was not adequately addressed herein is how to report the cost-effectiveness ratio. Certain jurisdictions require certain types of economic evaluations (e.g., cost-utility analysis in addition to cost-effectiveness analysis in Canada), but we recommend that economic evaluations should be performed to assist clinical and health-care policy decision making. Cost-effectiveness analysis should focus on the most relevant outcomes for decision making, rather than simply highlighting those aspects that make the investigational drug look the best.

The Panel on Cost-Effectiveness in Health and Medicine recently published a list of detailed recommendations for conducting health economic analysis [1]. In their recommendations, the panel considered a variety of different methodological techniques to improve the quality of future analyses and to encourage comparability across studies in general. Taking a different approach than the panel, this review highlights methodological discrepancies identified in cost-effectiveness analyses of antihypertensive agents. The following recommendations are therefore hypertension-specific but are considered to be consistent with the general recommendations provided by the panel:

- Cost-effectiveness analysis should be rigorous and useful for decision making.
- Short run outcomes should include systolic and diastolic blood pressure.
- Long-term outcomes should include, as appropriate, myocardial infarction, stroke, congestive heart failure and renal events depending on the length of follow-up. Long-term renal events may be useful only for very high-risk patients, as data

concerning the relationship of hypertension and renal events are scarce.
- Other positive attributes, such as a more favorable side-effect profile, should enhance (not replace) the long-term outcomes.
- When subpopulations are considered in submodels, studies should address limitations and generalizability issues.
- Modeling is an acceptable method provided that data sources and assumptions are valid and transparent.
- Cost calculations should be transparent and related to the perspective of the study.

Conclusion

Cost-effectiveness analyses should continue to be performed to address the economic impact of antihypertensive agents on this very costly disease. However, varying the methods used to estimate cost-effectiveness as a means for differentiating these agents is not appropriate and should not be confused with performing appropriate cost-effectiveness analyses to highlight true differences in product attributes. If different antihypertensive agents vary in their impact on the same long-term outcome, this should be highlighted in economic evaluations. In light of such disparity, economic analyses should be performed appropriately to aid the clinical and health-care policy decision-making process. If this is accomplished, we, as health services researchers, will feel secure knowing that our mission is possible and is beneficial to other health-care providers

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